REMARKS/ARGUMENTS

Status of the Claims

Upon entry of the present amendment, claims 74-109 are pending. Claims 74, 81 and 90 are amended to set forth *a* sample presenting surface. No new matter is added by the present amendments, and the Examiner is respectfully requested to enter them.

Telephonic Interview

Applicants thank Examiner Alexander for graciously granting the telephonic interview with Applicants' attorneys on April 11, 2006. The issues discussed during the interview are set forth below. During the interview, Applicants discussed how the present invention is novel and non-obvious over U.S. Patent No. 5,547,835 ("Köster"). Examiner Alexander indicated that Applicants' arguments would be considered.

In the interview summary mailed on April 13, 2006, it appears that the Examiner has misunderstood Applicants' arguments. Applicants discussed at length the significant physical differences between proteins and nucleic acid sequences. As discussed below, Köster is wholly devoted to sequencing nucleic acid sequences and does not disclose or suggest analyzing proteins whatsoever. Applicants pointed out to the Examiner that Köster discloses *cleaving* a *nucleic acid sequence* linked to a polymer support by a chemically cleavable linkage (*e.g.*, biotin-streptavidin) *before* subjecting the released nucleic acid sequence to mass spectrometry analysis. Köster does not disclose or suggest anywhere immobilizing a nucleotide or a protein to a mass spectrometry probe through a biotin-streptavidin linkage.

Rejection under 35 U.S.C. § 102(e)

Claims 74-108 stand rejected under 35 U.S.C § 102(e) as allegedly anticipated by U.S. Patent No. 5,547,835 ("Köster"). The Examiner alleged that Köster taught a method, apparatus and probe for laser desorption mass spectrometry using a biotin/streptabidin system for binding. Applicants respectfully traverse the rejection.

Applicants claim a probe for laser desorption/ionization mass spectrometry comprising a substrate having a sample presenting surface, a biotin-binding moiety (such as streptavidin) bound to the surface, a biotinylated protein bound to the biotin binding moiety and a matrix, which promotes desorption and ionization of intact proteins. Applicants' invention differs from Köster in several respects.

Köster does not teach or suggest a mass spectrometry probe having a biotin binding moiety attached to the surface

First, Köster does not show a mass spectrometry probe having a biotin binding moiety attached to the surface. Köster discloses a method in which nucleic acids are prepared (*i.e.*, purified) for analysis by mass spectrometry by first coupling the nucleic acids to a polymer support. (*See*, Köster, Figure 1.) However, in order to be analyzed by laser desorption mass spectrometry, the nucleic acids must first be cleaved from the polymer support. Köster discloses three ways to cleave the nucleic acids from the polymer support, each way characterized by a different binding mechanism. These three cleavage methods are set forth in Köster at column 13, lines 14-18, wherein Köster states that the DNA can be cleaved "enzymatically, chemically or physically." As examples of bonds subject to chemical cleavage, Köster provides disulfide bonds (cleavable with mercaptoethanol or dithioerythol) and a biotin/streptavidin system (cleavable under mildly acidic conditions). (*See*, Köster, column 13, lines 18-25.) As examples of bonds subject to enzymatic cleavage, Köster provides arginine-arginine or lysine-lysine bonds (cleavable with endopeptidase enzyme) and pyrophosphate bonds (cleavable with the enzyme pyrophosphatase). (*See*, Köster, column 13, lines 26-28.) As examples of bonds subject to physical cleavage, Köster provides photocleavable bonds, such as a charge transfer complex or a stable organic radical. (*See*, Köster, column 13, lines 28-30 and column 12, lines 4-10.) Köster does not provide any other specific examples of bonds subject to physical cleavage.

Köster characterizes chemical or enzymatic cleavage and photolytic cleavage as alternative processes. Chemical and enzymatic cleavage are performed before subjecting the nucleic acids to mass spectrometry. In contrast, photolytic cleavage is performed by using the laser to cleave the photolytic bond during mass spectrometry. Köster states:

> In addition to the examples given in which the nested fragments are coupled covalently to the solid support, washed, and cleaved off the support for mass spectrometric analysis, the temporary linkage can be such that it is cleaved under the conditions of mass spectrometry, i.e., a photocleavable bond such as a charge transfer complex or a stable organic radical. (column 12, lines 4-10.)

The alternative processes are further depicted in Figure 1, near the bottom of the figure.

Importantly, Köster classified the biotin-streptavidin bond as being chemically cleavable (*i.e.*, under acidic conditions), and not photolytically cleavable (*i.e.*, under conditions of mass spectrometry – subject to laser energy). Therefore, Köster does not teach or suggest using as a mass spectrometry probe a polymer support to which nucleic acids are bound through a biotin bond. Rather, Köster discloses *first* cleaving nucleic acids from the polymer support and *then* subjecting them to mass spectrometry.

Köster does not teach or suggest biotinylated proteins

Second, Köster is wholly directed to the sequencing of nucleic acid sequences. Köster does not disclose or suggest doing anything with proteins. The only mention of the term "protein" in Köster is in the context of titles of cited references within the specification (*see, for example*, column 6, line 32 and column 11, line 40). Köster discloses the attachment of biotinylated ***nucleic acids*** to a polymer support, which is not a mass spectrometry probe. In contrast, the claimed invention requires a biotinylated ***protein*** bound to the biotin binding moiety chemically bound to the mass spectrometry probe. As Applicants' attorneys discussed in the telephonic interview, nucleic acid sequences and proteins are distinct chemical classes – nucleic acid sequences being built of nucleotide building blocks and proteins being built of amino acid building blocks. Therefore, Köster does not disclose this element of the claims as nowhere in Köster is a biotinylated protein taught or suggested.

Summary

In sum, the present claims require a mass spectrometry probe comprising a sample presenting surface to which is bound a biotin binding moiety and a biotinylated protein

bound to the moiety, and further comprising a matrix for laser desorption/ionization mass spectrometry. Köster does not teach or suggest the cleavage of a biotin bond under mass spectrometry conditions, but rather by chemical cleavage, wherein the released nucleic acid sequences are *subsequently* subject to mass spectrometry analysis. Furthermore, Köster does not teach or suggest the capture of a biotinylated protein, because the object of analysis in Köster is sequencing nucleic acids. Therefore, Köster does not teach or suggest a probe, a method, or apparatus of this invention. For these reasons, Applicants respectfully request the Examiner to withdraw the rejection and allow this application to issue as a patent.

Rejection under 35 U.S.C. § 103(a)

Claim 109 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious over Köster in view of U.S. Patent No. 5,045,694 ("Beavis"). This rejection is respectfully traversed.

For the reasons discussed above, Köster does not teach or suggest a mass spectrometry apparatus comprising a mass spectrometry probe comprising a sample presenting surface to which is bound a biotin binding moiety and a biotinylated protein bound to the moiety, and further comprising a matrix for laser desorption/ionization mass spectrometry. Beavis does not supply the elements missing from Köster.

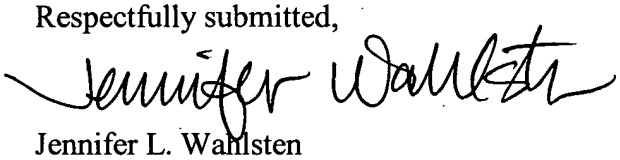
Therefore, the combined disclosures of Köster and Beavis do not render claim 109 obvious. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachments
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